An Efficient One-Pot Three Component Synthesis of 1,2-Dihydro-1-arylnaphtho[1,2-e][1,3]oxazine-3-ones Using Montmorillonite K10 under Solvent Free Conditions

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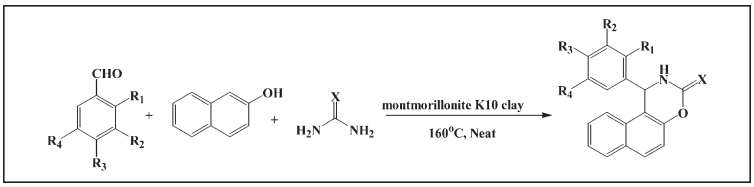

An efficient green protocol for the preparation of 1,2-dihydro-1-arylnaphtho[1,2-e][1,3]oxazine-3-ones employing a three-component one-pot condensation reaction of β-naphthol, aromatic aldehyde, urea or thiourea in the presence of montmorillonite K10 clay under solvent free conditions has been described. The present procedure offers advantages such as shorter reaction time (<90 min), simple workup, excellent yields, recovery and reusability of catalyst.

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INTRODUCTION

Recently, benzoxazinone derivatisation has attained considerable significance in potential antiviral target compounds [1]. The prime driving force in this area is the fight against HIV by developing more efficacious drugs than Efavirenz (Sustiva), a benzoxazinone derivative which is presently in clinical use for the treatment of AIDS.

The construction of new analogs of bioactive heterocyclic compounds represents a major challenge in synthetic organic and medicinal chemistry. Due to their broad spectrum of biological activities naphthalene-condensed 1,3-oxazin-3-ones have been reported to act as antibacterial agents [2]. Heterogeneous organic reactions have proven useful to chemists both in academia and in industry. Clay-catalyzed organic transformations have generated considerable interest because of their inexpensive nature and special catalytic attributes under heterogeneous reaction conditions [3].

In this context, a recent report [4] and related publications [5] on one pot three component synthesis of 1,2-dihydro-1-arylnaphtho[1,2-e][1,3]oxazine-3-ones by the condensation of aldehydes, urea or thiourea with β-naphthol in the presence of acid *p*-TSA attracted our attention. This method suffers from the drawbacks of green chemistry such as prolonged reaction times, recovery and reusability of catalyst. The demand for environmentally benign procedure with reusable catalyst necessitated us to develop an alternate method for the synthesis of 1,2-dihydro-1-arylnaphtho[1,2-e][1,3]oxazine-3-ones. In continuation of our work on the use of heterogeneous solid acid catalysts [6], we describe in this report a general and efficient green protocol for the preparation of 1,2-dihydro-1-arylnaphtho[1,2-e][1,3]oxazine-3-ones, employing a one-pot three-component condensation of β-naphthol, aromatic aldehydes urea or thiourea in the presence of montmorillonite K10 clay under solvent free conditions. This method is superior to the reported methods in all aspects such as short reaction times and excellent yields.

RESULTS AND DISCUSSION

Initially to determine the most appropriate reaction conditions and to evaluate the catalytic activity of Lewis/protic acid catalysts, a model study was carried out on the synthesis of 1,2-dihydro-1-arylnaphtho[1,2-e][1,3] oxazine-3-one **4a** (Table 1) by the condensation of benzaldehyde **1a** with β-naphthol **2** and urea **3a** in different sets of reaction conditions. Among all the tested catalysts such as Silica sulfuric acid, *p*-TSA, AcOH, LiCl, $CuCl_2$, $HClO_4$-SiO_2, Amberlist-15, and IR-120 under solvent free conditions we found that the best results were obtained with the condensation in the presence of montmorillonite K10 catalyst (Table 1, entry **1**).

The condensation of mixture of benzaldehyde **1a** (1 mmol) with β-naphthol **2** (1 mmol) and urea **3a** (1.5 mmol) in the presence of montmorillonite K10 (0. 3 mmol) was carried out at 160°C for 0.5 h under solvent free conditions (Scheme 1). The reaction proceeded

Table 1

Synthesis of 1,2-dihydro-1-arylnaphtho[1,2-e][1,3]oxazine -3-one 4a using different catalysts under solvent free conditions.

Entry	Catalyst	Yield (%)[b]	Ref
1	Montmorillonite K10 clay	89	–
2	Silica sulfuric acid	65	–
3	*p*-TSA	58	4
4	AcOH	45	4
5	LiCl	38	4
6	$CuCl_2$	30	4
7	$HClO_4$-SiO_2	64	–
8	Amberlist-15	48	–
9	IR120	44	–

[a] Benzaldehyde (1 mmol), urea (1.5 mmol), β-napthol (1 mmol), catalyst (0.3 mmol).
[b] Isolated yields.

smoothly and gave the corresponding 1,2-dihydro-1-aryl naphtho[1,2-e][1,3]oxazine-3-one **4a** as the sole product in 89% isolated yield. Ethyl acetate was added to the reaction mixture and simply filtering the mixture and evaporating the solvent from the filtrate gave the crude product, which was purified by crystallization in ethyl acetate: hexane (1:3) to obtain **4a** as white solid.

To evaluate the generality of the process, several examples illustrating the present method for the synthesis of 1,2-dihydro-1-arylnaphtho[1,2-e][1,3]oxazine-3-ones **4** was studied (Table 2). The reaction of β-naphthol **2** with various aromatic aldehydes bearing electron withdrawing groups (such as nitro, halide), electron releasing groups (such as methoxy, methyl or hydroxyl groups), and urea or thiourea was carried out in the presence of Montmorillonite K 10 as a catalyst.

The heterocyclic aldehydes such as furfural (entry m, Table 2) and 2-Chloroquinoline-3-aldehyde (entry n, Table 2) on reaction with β-naphthol **2** and urea **3** in the presence of montmorillonite K10 clay under solvent free conditions was sluggish and the corresponding products were isolated only in 10–15% yields. The poor reaction of heterocyclic aldehydes (entry m & n Table 2) with β-naphthol **2** can be explained by considering the possibility of binding of basic hetero atom (m & n) on the surface of Montmorillonite K10 clay. The results obtained in the current method are illustrated in Table 2. All products obtained were fully characterized by spectroscopic methods such as IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopy and also by comparison with the reported spectral data [4].

On the basis of all our experimental results, together with the literature reports [4], we have proposed the plausible mechanism for the formation of 1,2-dihydro-1-arylnaphtho[1,2-e][1,3]oxazine-3-ones **4** in the presence of Montmorillonite K10 clay (Scheme 2). The reaction is believed to proceed through the formation of an *N*-acylimine intermediate **5** formed *in situ* by the reaction of aldehyde **1** with urea or thiourea **3**. The subsequent addition of the β-naphthol to the *N*-acylimine, followed by cyclization affords the corresponding products **4**(a-p) and ammonia.

The simplicity, together with the use of inexpensive, non-toxic, and environmentally benign catalyst under solvent free condition is other remarkable features of the procedure. The catalyst was recovered by filtration, washed several times with methanol, dried at 120°C for 72 h and reused with out significant loss of catalyst activity.

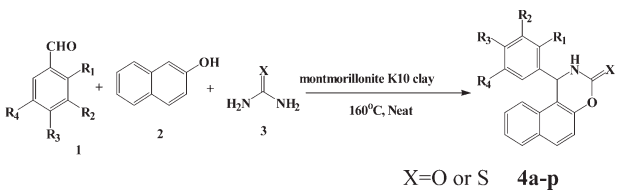
In conclusion, we have reported herein a novel and ecofriendly method for the synthesis of 1,2-dihydro-1-aryl naphtho[1,2-e][1,3]oxazine-3-ones using Montmorillonite K10 clay under solvent free conditions. The advantages of the present protocol are mild heterogeneous reaction conditions, shorter reaction times, and easy work up. The inexpensive, ready availability, recyclablity of the catalyst make the procedure an attractive alternative to the existing methods for the synthesis of 1,2-dihydro-1-arylnaphtho[1,2-e][1,3]oxazine-3-ones.

EXPERIMENTAL

General procedure. A mixture of β-naphthol (1 mmol), aldehyde (1 mmol), urea or thiourea (1.5 mmol) and Montmorillonite K10 clay (0.3 mmol) was rapidly stirred and heated at 160°C for the specified time (Table 2). After TLC indicates the disappearance of starting material, reaction was cooled to room temperature, ethyl acetate (25 mL) was added and the insoluble material was filtered to separate the catalyst. The filtrate was concentrated under vacuum and the crude residue was purified by crystallization in ethyl acetate: hexane (1:3) to afford pure product **4** in excellent yields as specified in Table 2. The catalyst filtered was washed with methanol (3 × 10 mL), dried at 120°C for 72 h and reused. The isolated product yields after each cycle is 78%. All products obtained were fully characterized by spectroscopic methods such as IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopy and have been identified by the comparison of the spectral data with those reported.

1-Phenyl-1,2-dihydronaphtho[1,2-e][1,3]oxazin-3-one (4a). m.p. 210–212°C, IR (KBr) ν_{max} 3281, 2928, 1727, 1627, 1514, 1458, 1435, 1396, 1338, 1289, 1221, 1165, 1111, 981, 925, 828, 745 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$ + DMSO-d_6): δ

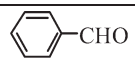
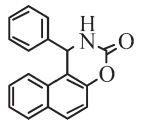
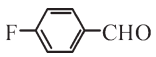
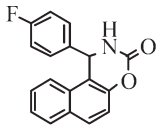
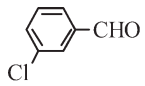
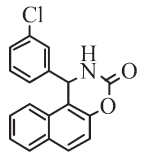
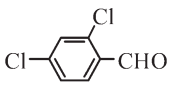
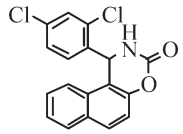
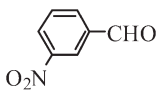
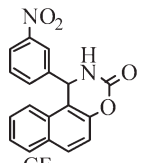
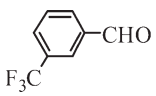
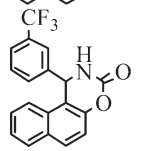
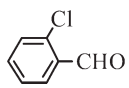
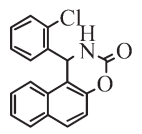
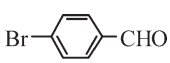
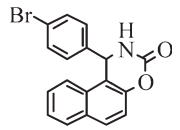
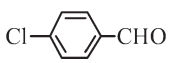
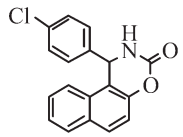
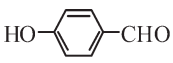
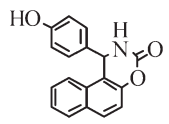
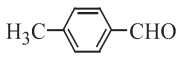
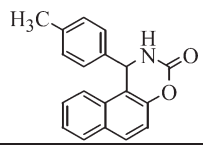
Scheme 1. X = O or S **4a-p.**



X=O or S **4a-p**

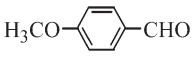
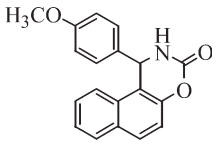
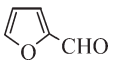
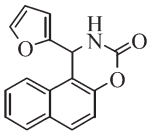
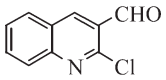
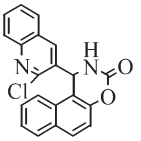
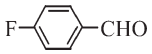
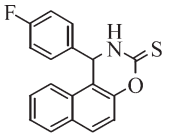
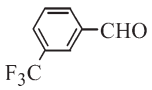
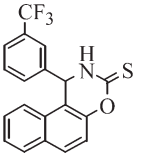
Table 2

Reaction of β-naphthol with various aldehydes and urea or thiourea.

Entry	Aldehyde **1**	Urea/Thiourea **3**	Product **4**	Reaction Time (min)	Yield[a] (%)
a		NH_2CONH_2		30	89
b		NH_2CONH_2		30	84
c		NH_2CONH_2		55	85
d		NH_2CONH_2		50	90
e		NH_2CONH_2		30	79
f		NH_2CONH_2		30	85
g		NH_2CONH_2		45	84
h		NH_2CONH_2		60	75
i		NH_2CONH_2		45	72
j		NH_2CONH_2		90	70
k		NH_2CONH_2		90	72

(*Continued*)

Table 2
(*Continued*)

Entry	Aldehyde **1**	Urea/Thiourea **3**	Product **4**	Reaction Time (min)	Yield[a] (%)
l		NH_2CONH_2		90	70
m		NH_2CONH_2		90	15
n		NH_2CONH_2		90	10
o		NH_2CONH_2		45	64
p		NH_2CONH_2		45	65

[a] Field of isolated products.

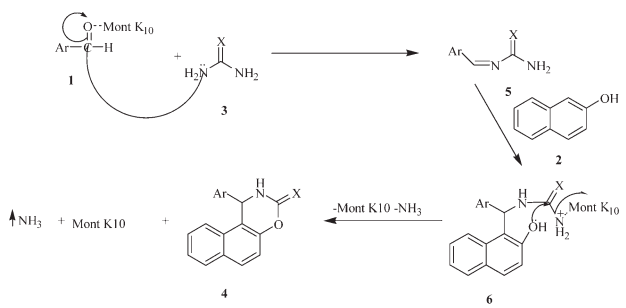
6.04 (d, J = 3.12 Hz, 1H), 7.26–7.40 (m, 7H), 7.56–7.64 (m, 2H), 7.78–7.86 (m, 2H), 8.56 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$ + DMSO-d_6): δ 56.4, 113.8, 117.6, 123.4, 125.0, 127.4, 127.8, 127.9, 129.2, 129.5, 129.9, 131.0, 131.3, 142.0, 148.1, 150.1. MS (ESI) m/z 276 ([M + H]$^+$). Anal. Calcd for $C_{18}H_{13}NO_2$: C, 78.53; H, 4.76; N, 5.09. Found: C, 78.53; H, 4.75; N, 5.09.

1-(4-Fluorophenyl)-1,2-dihydronaphtho[1,2-e][1,3] oxazin-3-one (4b). m.p. 199–200°C. IR (KBr) ν_{max} 3427, 3215, 3127, 2955, 1750, 1627, 1509, 1396, 1224, 1180, 808, 736 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$ + DMSO-d_6): δ 6.02 (d, J = 2.29 Hz, 1H), 6.93–7.01 (m, 2H), 7.22–7.54 (m, 6H), 7.79–7.86 (m, 2H), 8.54 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$ + DMSO-d_6): δ 52.9, 112.0, 114.3, 114.8, 115.7, 121.5, 123.9, 126.2, 127.5, 127.8, 127.9, 129.1, 129.5, 137.2, 146.6, 148.7, 158.4, 163.3. MS (ESI) m/z 294 ([M + H]$^+$). Anal. Calcd for $C_{18}H_{12}FNO_2$: C, 73.71; H, 4.12; N, 4.78. Found: C, 73.72; H, 4.11; N, 4.77.

1-(3-Chlorophenyl)-1,2-dihydronaphtho[1,2-e][1,3]oxazin-3-one (4c). m.p.192–195°C. IR (KBr) ν_{max} 3433, 3348, 2923, 1752, 1678, 1623, 1464, 1384, 1222, 1177 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$ + DMSO-d_6): δ 6.07 (d, J = 2.93 Hz, 1H), 7.22–7.56 (m, 7H), 7.78–7.90 (m, 3H), 8.72 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$ + DMSO-d_6): δ 52.8, 111.4, 115.4, 121.2, 123.7, 124.1, 125.7, 126.1, 126.8, 127.3, 127.6, 129.1, 132.8, 143.1, 146.4, 148.3, 154.5. MS (ESI) m/z 310 ([M + H]$^+$). Anal. Calcd for $C_{18}H_{12}ClNO_2$: C, 69.80; H, 3.90; N, 4.52. Found: C, 69.79; H, 3.91; N, 4.52.

1-(2,4-Dichlorophenyl)-1,2-dihydronaphtho[1,2-e][1,3]oxazin-3-one (4d). m.p.239–242°C. IR (KBr) ν_{max} 3244, 3141, 1737, 1627, 1623, 1586, 1468, 1393, 1287, 1225, 1117, 748 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$ + DMSO-d_6): δ 6.48 (d, J = 3.12 Hz, 1H), 6.96–7.08 (m, 2H), 7.28–7.52 (m, 5H), 7.81–7.89 (m, 2H) 8.29 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$ + DMSO-d_6): δ 50.2, 111.0, 115.7, 121.1, 124.1, 126.6, 127.2, 127.7, 127.9, 128.4, 129.3, 129.7, 132.0, 133.3, 137.0, 147.0, 148.4. MS (ESI) m/z 344 ([M + H]$^+$). Anal. Calcd for $C_{18}H_{11}Cl_2NO_2$: C, 62.81; H, 3.22; N, 4.07. Found: C, 62.82; H, 3.22; N, 4.06.

Scheme 2. Plausible mechanism for the formation of 1,2-dihydro-1-arylnaphtho[1,2-e][1,3]oxazine-3-ones 4.



1-(3-Nitrophenyl)-1,2-dihydronaphtho[1,2-e][1,3] oxazin-3-one (4e). m.p. 228–230°C, IR (KBr) ν_{max} 3380, 3065, 2924, 1727, 1627, 1594, 1527, 1346, 1221, 1176, 810, 744 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$ + DMSO-d_6): δ 6.42 (d, J = 2.34 Hz, 1H), 7.31–7.95 (m, 8H), 8.32–8.35 (m, 2H), 8.86 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$ + DMSO-d_6): δ 52.3, 110.9, 115.6, 120.9, 121.2, 121.7, 123.9, 126.3, 127.4, 127.6, 128.9, 129.3, 129.4, 132.0, 143.0, 146.9, 148.2. MS (ESI) m/z 321 ($[M + H]^+$). Anal. Calcd for $C_{18}H_{12}N_2O_4$: C, 67.50; H, 3.78; N, 8.75. Found: C, 67.49; H, 3.78; N, 8.76.

1-(3-Trifluoromethylphenyl)-1,2-dihydronaphtho [1,2-e][1,3] oxazin-3-one (4f). m.p. 251–253°C, IR (KBr) ν_{max} 3446, 3248, 2924, 1752, 1705, 1631, 1592, 1517, 1395, 1321, 1223, 1171, 1113, 1064, 920, 813, 738 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$ + DMSO-d_6): δ 6.15 (d, J = 2.93 Hz, 1H), 7.28–7.55 (m, 7H), 7.72 (s, 1H), 7.82–7.90 (m, 2H), 8.76 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$ + DMSO-d_6): δ 53.0, 111.4, 115.7, 120.0, 121.3, 122.9, 123.7, 124.0, 126.4, 127.6, 127.9, 128.6, 129.5, 142.2, 146.8, 148.6. MS (ESI) m/z 344 ($[M + H]^+$). Anal. Calcd for $C_{19}H_{12}F_3NO_2$: C, 66.47; H, 3.52; N, 4.08. Found: C, 66.48; H, 3.52; N, 4.08.

1-(2-Chlorophenyl)-1,2-dihydronaphtho[1,2-e][1,3] oxazin-3-one (4g). m.p. 222–224°C, IR (KBr) ν_{max} 3393, 3059, 2925, 1741, 1583, 1438, 1372, 1231, 1123, 1042, 976, 784, 746 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$ + DMSO-d_6): δ 6.54 (d, J = 1.46 Hz, 1H), 7.12–7.52 (m, 8H), 7.83–7.88 (m, 2H), 8.10 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$ + DMSO-d_6): δ 50.4, 111.4, 115.6, 121.2, 123.9, 126.4, 126.8, 127.5, 127.9, 128.1, 128.5, 128.6, 129.3, 131.0, 138.2, 146.8, 148.4. MS (ESI) m/z 310($[M + H]^+$). Anal. Calcd for $C_{18}H_{12}ClNO_2$: C, 69.80; H, 3.90; N, 4.52. Found: C, 69.79; H, 3.90; N, 4.51.

1-(4-Fluorophenyl)-1,2-dihydronaphtho[1,2-e][1,3]oxazine-3-thione (4o). Thick syrup; IR (KBr) ν_{max} 3060, 2923, 1628, 1600, 1508, 1460, 1390, 1267, 1216, 1162, 1016, 843, 811, 750 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$ + DMSO-d_6): δ 4.37 (s, 1H), 6.84–7.82 (m, 10H), 9.22 (brs, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 29.7, 109.4, 115.0, 115.2, 117.7, 123.1, 123.5, 126.3, 126.4, 126.6, 127.6, 128.5, 129.4, 129.5, 129.7, 151.0, 153.3. MS (ESI) m/z 360 ($[M + H]^+$). Anal. Calcd for $C_{18}H_{12}FNOS$: C, 69.88; H, 3.91; N, 4.53. Found: C, 69.88; H, 3.91; N, 4.54.

1-(3-Trifluoromethylphenyl)-1,2-dihydronaphtho [1,2-e][1,3] oxazine-3-thione (4p). Thick syrup; IR (KBr) ν_{max} 3240, 3052, 2923, 1627, 1512, 1443, 1327, 1263, 1165, 1121, 1071, 845, 742 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$ + DMSO-d_6): δ 4.45 (s, 1H), 7.02–7.86 (m, 10H), 9.10 (brs, 1H). ^{13}C NMR (50 MHz, $CDCl_3$ + DMSO-d_6): δ 30.0, 108.7, 116.8, 117.9, 118.2, 122.4, 122.5, 124.6, 125.7, 127.2, 127.8, 128.2, 128.8, 131.6, 133.1, 134.4, 142.2, 152.5, 154.8. MS (ESI) m/z 360 ($[M + H]^+$). Anal. Calcd for $C_{19}H_{12}F_3NOS$: C, 63.50; H, 3.37; N, 3.90. Found: C, 63.51; H, 3.37; N, 3.91.

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